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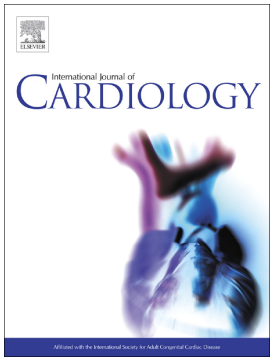

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Restarting Oral Anticoagulant Therapy after Major Bleeding in Atrial Fibrillation: A Systematic Review and Meta-Analysis

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Dr Marco Proietti and Prof Gregory YH Lip take responsibility for all aspects of the reliability and freedom of bias of the data presented and their discussed interpretation.

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AUTHORS CONTRIBUTIONS

MP, GFR and GYHL conceived and designed the study; GFR and IR performed the search; MP, GFR and IR performed the studies selection; MP and GFR extracted the data and performed the bias assessment; MP and AF performed the statistical analysis; MP produced the first draft manuscript; GFR and GYHL contributed to the drafting of the manuscript; LS and PBN critically revised the manuscript for important intellectual content. MP and GYHL are guarantors of the paper. All authors read and approved the final version of the manuscript.

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MP has received small consulting fee from Boheringer Ingelheim; LS has received a restricted grant from Boheringer Ingelheim; PBN has served as a speaker for Boehringer Ingelheim and consultant for Bayer and received unrestricted research grant from BMS/Pfizer; GYHL has served as consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No fees are received personally. Other authors have no disclosures to declare.

Keywords: atrial fibrillation; major bleeding; restarting; oral anticoagulant therapy.

ABSTRACT

Background: Use of oral anticoagulant (OAC) therapy in atrial fibrillation (AF) is associated with an inherited risk of bleeding. Benefits and risks of OAC restarting after a major bleeding are still uncertain. We aimed to assess effectiveness and safety of restarting OAC in AF patients after a major bleeding event.

Methods: We performed a systematic review and meta-analysis of all studies reporting data about AF patients that sustained a major bleeding, reporting data on restarting or not restarting OAC therapy.

Results: A total of seven studies were included, involving 5685 patients. No significant difference was found in 'any stroke' occurrence between OAC restarters and non-restarters (odds ratio [OR]: 0.75, 95% confidence interval [CI]: 0.37-1.51), with a significant 46% relative risk reduction (RRR) ($p<0.00001$) for 'any thromboembolism' in OAC restarters, with consistent results when the index bleeding event was an intracranial or gastrointestinal bleeding. A significantly higher risk of recurrent major bleeding was seen (OR: 1.85, 95% CI: 1.48-2.30), but no difference in risk for recurrence of index event. OAC restarters had a 10.8% absolute risk reduction for all-cause death (OR: 0.38, 95% CI: 0.24-0.60); $p<0.00001$). Net clinical benefit (NCB) analysis demonstrated that restarting OAC therapy after a major bleeding was significantly associated with a clinical advantage (NCB: 0.11, 95% CI: 0.09-0.14; $p<0.001$).

Conclusions: Restarting OAC therapy after a major bleeding event in AF was associated with a positive clinical benefit when compared to non-restarting OAC, with a significant reduction in any thromboembolism and all-cause mortality.

1. INTRODUCTION

Oral anticoagulant (OAC) therapy represents the mainstay for stroke prevention in atrial fibrillation (AF)[1]. At the same time, an unavoidable bleeding risk is associated with OAC use[2–4]. A prior history or occurrence of a major bleeding event is associated with several risk factors for stroke as well as a higher risk for a recurrent major bleeding occurrence[5]. All current clinically-based bleeding risk scores include history of bleeding among the risk factors considered[6–9].

Decision to restart OAC after a major bleeding event still remains a highly debated topic. In the 2016 European Society of Cardiology (ESC) AF guidelines, restart of OAC after a major bleeding/intracranial hemorrhage (ICH) event is currently recommended, after a careful evaluation of clinical status, but this recommendation was based on a low level of evidence[10]. A recent position paper from ESC Working Group on Thrombosis recommended restart of OAC after both extracranial and intracranial bleeding, after careful evaluation and consideration of other thromboembolic and bleeding concurrent risk factors[11]. Notwithstanding, these consensus recommendations are all based on limited evidence from observational studies or deduced from other cohorts of non-AF patients[11].

Our aim for this systematic review and meta-analysis was to review available evidence about restarting OAC in AF patients after an OAC-related major bleeding event (any major bleeding, any ICH, any gastrointestinal bleeding [GIB]) and its association with subsequent major adverse events. We also performed a net-clinical benefit (NCB) analysis to elucidate the benefit-risk balance of restarting OAC.

2. METHODS

The present systematic review and meta-analysis was performed according to PRISMA recommendations (http://www.prisma-statement.org/).

2.1 Data Sources and Searches

We performed a comprehensive literature search using PubMed and Scopus databases up to 31st of December 2017. Search terms included 'atrial fibrillation', 'major bleeding', 'gastrointestinal bleeding', 'gastrointestinal hemorrhage', 'intracranial hemorrhage', 'brain hemorrhage', 'hematemesis', 'melena'. Full search strategy has been reported in S1 Methods. The electronic search was carried out for peer-reviewed journals and, if applicable, some further additional references were gathered from searches through bibliographies of identified papers and from authors' personal knowledge.

After search, all results have been screened by two co-authors independently (GFR and IR). Disagreements were resolved by collegial discussion with a third co-author (MP). All articles retrieved from the search were evaluated according to titles (mostly excluding not original data papers, commentaries, viewpoints and all entries that clearly did not qualify for inclusion), abstract and full-text evaluation, sequentially. Studies for which it was possible to clearly ascertain a relevant overlap of cohorts were evaluated according to time of data collection and/or year of publication; accordingly, data collected and/or published more recently were included in the analysis.

2.2 Study Selection

To perform our systematic review and meta-analysis, the following selection criteria for studies were considered: (i) all studies should report on patients with AF treated with OAC

prior to the occurrence of a major bleeding with at least one hundred patients enrolled as study cohort; (ii) where possible, we extracted data on location of index bleeding event, and data with reporting and comparisons of patients restarting and non-restarting OAC after the bleeding index event; and (iii) available data on major adverse events on follow-up observations. Exclusion criteria were: i) conference abstracts, letters, comments, case reports, and editorials; and ii) studies not published in English.

2.3 Data Extraction and Quality Assessment

Data were extracted independently by two of the co-authors (MP and GFR). All data on sample size of restarting and non-restarting OAC subgroups, number of major adverse events, incidence rates or measures of effect were collected. Data about study characteristics, age, bleeding and thromboembolic risk were also collected when available. Outcomes considered were: any stroke (defined as any ischemic stroke plus transient ischemic attack) and/or any thromboembolic event (any stroke plus any systemic thromboembolic events), recurrent major bleeding and/or recurrent index bleeding event and all-cause death. All studies were evaluated independently to assess risk of bias by two co-authors (MP and GFR), according to recommendations of Agency for Healthcare Research and Quality[12]. Evaluation was performed for selection, performance, attrition, detection and reporting bias categories. Finally, an overall evaluation was done. All studies have been categorised as low, moderate or high risk of bias. Given the low numbers of studies considered (<10 studies), publication bias evaluation was not performed to avoid unreliable results.

2.4 Data Synthesis and Analyses

All statistical analyses were performed using Review Manager 5.3 (The Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark) and R 3.4.0 (R

Development Core Team, Vienna, Austria). Risk of events according to OAC restarting was reported as odds ratio (OR) and 95% confidence interval (CI), relative risk reduction (RRR) or absolute risk reduction. To assess the clinical benefits and risks of restarting OAC after a major bleeding event, we performed a NCB analysis. Full details about statistical analysis and NCB analysis have been reported in S1 Methods.

3. RESULTS

Our literature search retrieved 10013 results from PubMed and Scopus databases. After our selection process [Figure S1], a total of 7 studies[13–19] were included in the systematic review and in the final meta-analysis (Table 1). In one study, any major bleeding was the bleeding index event[13], two papers considered ICH[14,15] and four papers considered GIB[16–19] as the index event. Six out of seven studies were retrospective longitudinal analysis of observational cohorts, with only one small prospective study, focused on GIB[19]. All the studies included patients characterized by both high bleeding and thromboembolic risks (Table 1). In all the studies, except for Hernandez et al[13] as detailed below, all patients were restarted only with vitamin K antagonists

3.1 Overview of Included Studies

In the paper by Hernandez and colleagues[13], 1539 AF patients among the Medicare Part D beneficiaries reported a major bleeding episode from 2010 to 2012. Of these 1135 (73.7%) were treated with warfarin before the index event, while 404 (26.3%) were treated with dabigatran. In the overall cohort, 167 (10.9%) patients reported an ICH, 1111 (72.2%) GIB, 73 (4.7%) genitourinary bleeding and 188 (12.2%) had other type of bleeding. The overall cohort had both a high thromboembolic (CHA_2DS_2-VASc >2) and bleeding (HAS-BLED ≥3) risk.

After the bleeding event, 843 (54.8%) of the patients did not restart OAC therapy. Among restarters, 95 (6.2%) switched OAC (warfarin to dabigatran or dabigatran to warfarin) and 601 (39.0%) restarted the same OAC[13]. After 1 year of follow-up, all patients restarted on OAC, both warfarin and dabigatran had a significant reduction in risk for all-cause death (hazard ratio [HR]: 0.35, 95% CI: 0.23-0.53 and HR: 0.13, 95% CI: 0.04-0.41, respectively) and ischemic stroke/all-cause death composite outcome (HR: 0.76, 95% CI: 0.59-0.97 and HR: 0.66, 95% CI: 0.44-0.99, respectively). Patients restarted on warfarin had also an increased risk of major recurrent bleeding (HR: 1.56, 95% CI: 1.10-2.22). Comparing patients restarted on dabigatran with those restarted on warfarin, patients on dabigatran had a lower risk for major recurrent bleeding (HR: 0.42, 95% CI: 0.21-0.84)[13].

Both the papers examining OAC restart after ICH found that patients restarting OAC after the index event reported a significantly lower risk of thromboembolic events[14,15]. Furthermore, both documented an improved survival for patients restarting OAC [14,15]. Contrary to what was described by Kuramatsu et al[14], Nielsen et al documented a variable extent of increased bleeding risk[15]. Indeed, their original study cohort comprised both patients that reported spontaneous hemorrhagic stroke and traumatic ICH[15]. While patients with traumatic ICH had a lower relative risk of recurrent ICH, those patients that reported spontaneous hemorrhagic stroke reported an increased relative risk of recurrent event[15]. Due to limited power, the authors did not fully assess the relationship between OAC resumption and recurrent bleeding[15].

All the studies investigating OAC restart after GIB consistently reported that patients restarted on OAC had a lower risk of thromboembolic events [16–19] and a lower risk of all-

cause death[16–18] (except for the study by Sengupta et al.[19]), even though for two of these studies, only around 50% of patients were prescribed OAC due to AF.

For the risk of recurrent bleeding, in the two studies reporting cohorts with mixed indications for OAC (~50% of AF patients) there was a numerically higher risk of recurrent GIB, and after multiple adjustments these differences became not significant[16,19]. In the study by Qureshi and colleagues, that selected non-valvular AF patients surviving a GIB event and interrupted OAC for at least 72 hours, those patients that restarted OAC therapy within the first seven days had an increased risk of recurrent GIB compared to those that restarted after 30 days or more (HR: 3.27, 95% CI: 1.82-5.91), while for all other patients, restarting at different time-points, there was no increased risk of bleeding[17].

The paper by Staerk et al. included 4602 AF patients discharged after an OAC related GIB and after a 90 days blanking period, 3409 were included in the study. Of these, 924(27.1%) did not restart any antithrombotic drug, while 725(21.3%) were restarted on single OAC therapy, 1314(38.5%) were restarted on single antiplatelet therapy and 446(13.1%) were restarted on double and triple antithrombotic therapy[18]. Over the 2 years follow-up, patients restart single OAC and OAC plus antiplatelet therapy both reported an increased risk of recurrent major bleeding events (HR: 1.37, 95% CI: 1.06-1.77 and HR: 1.44, 95% CI: 1.00-2.08, respectively)[18]. Sensitivity analyses investigating shorter and longer blanking periods, found out a more relevant risk for recurrent major bleeding was evident in patients restarted on single antiplatelet therapy. The authors did not report any increase in risk of recurrent GIB, irrespective of any blanking period and any antithrombotic therapy regimen[18].

Regarding the timing of OAC restarting, very few data were provided. Only in the paper by Qureshi et al. a stratified analysis according to time to restart was performed. As reported above, patients restarting very early were burdened by a significant risk of recurrent GIB, even though a concomitant significant reduction in all-cause death occurrence (HR: 0.56, 95% CI: 0.33-0.93) was found when compared to those patients that restarted after 30 days or more after the index bleeding[17]. In the study by Hernandez and colleagues, patients restarted with warfarin reprised the treatment within 60 to 73 mean days after index event, while patients restarted with dabigatran restarted treatment within 45 to 70 mean days, with patients restarted with dabigatran reporting a higher risk for recurrent major bleeding[13]. In the study by Nielsen and Kuramatsu, OAC were restarted after mean and median 31 days, respectively[14,15]. In the two studies investigating short-term follow-up, patients were restarted on OAC, respectively after 4 and 5 days in the studies by Witt and Sengupta[16,19].

3.2 Risk of Bias Evaluation

According to the methods, a risk of bias evaluation was performed (Table S1). Two studies reported a high risk of bias, mainly due to both selection and reporting bias. All the other studies have been categorized as with a low risk of bias.

3.3 Meta-Analysis of Included Studies

Based on the inclusion criteria all relevant data were extracted from the selected studies. From the papers by Witt[16] and Sengupta[19], data on the AF subgroup were extracted, with only data regarding stroke and any thromboembolic event retrieved. From the paper by Nielsen and colleagues[15], due to the uncertainty of treatment assignment related to the time-dependent design, a restricted cohort of patients was selected to be included in the meta-analysis. Then, the propensity-matched cohort of patients assigned to OAC restarting and

OAC non-restarting after 10 weeks of blanking period was pooled together with the other studies. From the paper by Staerk et al.[18], we only included those patients restarted on OAC only, given the aim of this meta-analysis. A total of 5685 patients were therefore included in our meta-analysis (Table 1).

3.3.1 Effectiveness Outcomes

Overall, 3626 patients were considered for analysis of the 'any stroke' occurrence outcome [Figure 1, Panel a]. Of these, 1402(38.7%) were restarted with OAC. There was a total of 128(9.1%) any stroke events in those patients that restarted OAC, while 184(8.3%) events were reported among non-restarters. Pooling all data together found no difference in the risk of any stroke occurrence between OAC restarters and non-restarters (OR: 0.75, 95% CI: 0.37-1.51); however, there was a significant lower risk for GIB patients (p=0.04). A 45% relative risk increase was found in those patients with 'any major bleeding' (p=0.02), with a significant difference between 'any major bleeding' and GIB subgroups (p=0.02).

For the endpoint of any thromboembolic event [Figure 1, Panel b], 8.0%(149) of events were recorded in OAC restarters, while 12.2%(277) of events were recorded in non-restarters. In the pooled analysis, a significant 46% RRR was found (p<0.00001) in OAC restarters compared with non-restarters. The observed association was consistent between patients that reported ICH and GIB as index bleeding events (55% RRR and 44% RRR, respectively).

3.3.2 Safety Outcomes

A total of 5347 patients were included in the analysis for safety outcomes [Figure 2]. In the group of OAC restarters there were a total of 242(10.2%) recurrent major bleeding events, while in OAC non-restarters 150 patients (5.0%) had a recurrent major bleeding event.

Overall, there was an increased risk (OR: 1.85, 95% CI: 1.48-2.30) for recurrent major bleeding in OAC restarters [Figure 2, Panel a]. When we considered the recurrence of index bleeding event [Figures S2-S3], there was no significantly increased risk of ICH (p=0.77) or GIB (p=0.16).

For all-cause death, there was a 10.8% absolute risk reduction in the group of OAC restarters, and the pooled analysis found a marked reduction in risk of all-cause death (OR: 0.38, 95% CI: 0.24-0.60).

3.3.3 Sensitivity Analysis

According to risk of bias, a bias-stratified sensitivity analysis was performed for any stroke and any thromboembolic event occurrence [Figures S4-S5]. Bias-stratified analysis was not performed for recurrent major bleeding and all-cause death outcomes since all the studies included in the main analysis were those ones with low risk of bias.

For any stroke occurrence [Figure S4], 'high risk of bias' studies reported a significant risk reduction (OR: 0.10, 95% CI: 0.01-0.86), but overall no difference in risk was found between OAC restarters and non-restarters (OR: 0.71, 95% CI: 0.34-1.46). For any thromboembolic event occurrence, despite a strong influence of 'high risk of bias' studies in determining a significant association (with a strong trend in subgroup differences, p=0.07) [Figure S5], the 'low risk of bias' studies subgroup still showed a significant RRR (p<0.00001).

3.4 Net Clinical Benefit Analysis

Due to lack of data about recurrent bleeding and all-cause death occurrence, two studies were not included in this analysis[16,19]. Based on the original data, incidence rates for every

outcome considered were calculated and used to compute the NCB analysis models (Table S2).

In the first NCB model, which was constructed balancing only the endpoints of any stroke/any thromboembolic event and recurrent major bleeding, we did not find any significant difference between OAC restarters and OAC non-restarters (p=0.881) [Figure 3, Upper Panel]. In the second NCB model [Figure 3, Lower Panel], in which risk of occurrence for all-cause death was balanced with any stroke/any thromboembolic event and recurrent major bleeding, there was a significant clinical advantage in restarting OAC (NCB: 0.11, 95% CI: 0.09-0.14; p<0.001).

For both models, separated sensitivity analyses were performed. In the first model, varying the relative weight for recurrent major bleeding between 0.2 and 1.5 in an equidistant grid of 1000 values, the signs agreed for 4 studies out of 5 in 100% of the cases, while only for the study by Nielsen and colleagues in 40% of the cases there was a sign discordance and therefore a weight dependency. In the second model, for each possible combination of any stroke/any thromboembolic event and recurrent major bleeding weights, equally spaced between 0.1 and 1 (10000 possible combinations), the signs agreed for at least 4 studies out of 5 in 98.6% of cases. Only for study by Qureshi et al. there was in 44% of cases, a sign discordance and therefore a weight dependency. Repeating the NCB analyses, excluding those studies that demonstrated a weight dependency, provided non-significantly different results (data not shown).

4. DISCUSSION

In this systematic review and meta-analysis, we provided evidence using data from more than 5000 patients that restarting OAC therapy in AF patients after occurrence of a major bleeding event is significantly associated with lower clinical adverse events. Indeed, restarting OAC after a major bleeding event provided a significant risk reduction from any thromboembolic event and mortality, compared with patients that did not restart OAC therapy. Despite an increase in risk of recurrent major bleeding, the risks for recurrent ICH or recurrent GIB was similar between OAC restarters and non-restarters. Importantly, there was a 62% RRR for all-cause death, with an absolute risk reduction of more than 10%. Finally, the NCB analysis demonstrated that OAC restarting was not associated with an increased risk of major bleeding, but conversely was associated with an overall positive effect on the clinical course of AF patients after the occurrence of a major bleeding event.

Since the introduction of non-vitamin K antagonist oral anticoagulants for stroke prevention in AF, the safety of OAC treatment has improved[20]. Use of non-vitamin K antagonist oral anticoagulants was found associated with 14% RRR for major bleeding occurrence, with a particular reduction in risk for ICH occurrence, even though a significant increase in GIB was found[20]. Despite the improved safety, the risk of bleeding remains a relevant clinical risk[3].

Once the bleeding event has occurred, the management of OAC therapy becomes more uncertain, especially since many randomised trials exclude patients with a recent bleeding event. Indeed, data from the "Outcomes Registry for Better Informed Treatment of Atrial Fibrillation" study showed that previous bleeding was the more prevalent reason for which

physicians withhold OAC therapy (27.7%), and in 20% of the cases a previous bleeding was the main reason reported for OAC discontinuation[21].

In a recent single centre cohort study from a tertiary Spanish Hospital anticoagulation clinic, the occurrence of major bleeding during follow-up was found independently associated with a 5-fold increase in the risk of discontinuing OAC[22]. After discontinuation, a significantly increase in risk for ischemic stroke occurrence (HR: 1.85, 95% CI: 1.17-2.94), cardiovascular events (HR: 1.45, 95% CI: 1.01-2.08) and all-cause death (HR: 1.30, 95% CI: 1.02-1.67) was seen, without any significant benefit in terms of major bleeding occurrence[22]. Our study demonstrates that even after the occurrence of a major bleeding event, OAC restarting was associated with an increase in recurrent major bleeding, but with an associated positive NCB in favour of restarting OAC treatment due to a significant reduction in thromboembolic events and all-cause death.

Recently, Murthy and colleagues presented a meta-analysis about restarting OAC after ICH occurrence, including highly heterogeneous studies, most of which enrolled patients with mixed indications and varying percentages of patients with AF (from 34.7% to 100.0%)[23]. However, Murthy and colleagues had broadly similar results to those reported in our study, with a significant reduction in risk of thromboembolic events, without any increase in the risk of recurrent ICH[23]. Another meta-analysis analysing studies about patients reporting a GIB occurrence, reported broadly similar results, also with a significant reduction in risk of all-cause death [24]. Our results strengthen those observations, underlining and reinforcing the effectiveness and safety of restarting OAC therapy specifically in AF patients with an overall clear significant NCB.

Currently, ESC guidelines recommend restarting OAC after major bleeding events, despite reporting a low level of evidence (Class IIa, Level B) and based exclusively on the study presented by Kuramatsu and colleagues, and recommending a multidisciplinary team approach during the decision-making process[10]. In regard to ICH, restarting of OAC is recommended with an even lower level of evidence (Class IIb, Level B), being based on expert opinion and small heterogeneous studies, with only one study reported about AF patients[10]. Similarly, the ESC Working Group on Thrombosis, despite recommending the re-initiation of OAC therapy, all recommendations are based on very limited data about AF patients[11]. The evidence provided by our meta-analysis is able to confirm these recommendations, substantiating and reinforcing these consensus recommendations, by considering the net advantage demonstrated in reduction of thromboembolic events and all-cause death.

Despite providing a strong evidence of effectiveness and safety of OAC restarting, our data were based only on observational studies. Thus, adequately powered randomized clinical trials or prospective cohorts are needed to confirm our observations. For example, the "Apixaban versus Antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intraCerebral HaEmorrhage in patients with Atrial Fibrillation" study is a randomized controlled trial investigating the effect of apixaban (either 5 mg or 2.5 mg bid) vs. single or double antiplatelet therapy vs. no antithrombotic treatment[25] (http://www.apache-af.nl). This is a phase II, randomised, open-label, parallel-group, multicentre clinical trial with masked outcome assessment, aiming to enrol non-valvular AF patients with a high thromboembolic risk (CHA_2DS_2-VASc ≥ 3) that reported an ICH event, randomizing them to one of the three arms within 7 and 90 days after the index event followed up for at least 1 year after randomization. Primary outcome will be the combination

of vascular death or non-fatal stroke[25] (ClinicalTrials.gov NCT02565693). Results from this trial, as well as from other future randomized clinical trials, will be helpful to present more reliable evidence and confirm results provided from our study.

Uncertainties still remain about timing of restarting OAC therapy. ESC guidelines recommend restarting within 4 to 8 weeks after ICH event. In our systematic review, there was a large heterogeneity of restarting time after index bleeding event. Hernandez and colleagues reported a slightly later restarting time when warfarin was chosen, with an increased risk of bleeding associated with warfarin use. The studies by Kuramatsu[14] and Nielsen[15], in which OAC was restarted approximately after 4 weeks, did not underline a significant difference in recurrent bleeding risk, except for patients with a traumatic ICH[15]. Two of the studies resuming OAC very early on did not show any difference in terms of recurrent bleeding risk[16,19]. Conversely, in the study by Qureshi et al. evidence was provided that early restart was associated with an increased risk of recurrent bleeding[17]. Other two studies by the same group tried to investigate in two heterogeneous cohorts, the optimal timing of OAC resumption after ICH and GIB[26,27]. In the first paper, enrolling 234 patients with an ICH (58% with AF as indication for OAC), the authors found out that the combined risk of a recurrent ICH and an ischemic event reached a nadir when OAC was restarted between 10 and 30 weeks[26]; in the second paper, a risk modelling analysis based on 207 patients (63%) with a GIB event, found that the nadir between the recurrent bleeding and thromboembolic occurrence risk was reached restarting the OAC between 3 and 6 weeks[27]. Currently, our meta-analysis does not provide evidence to specifically support a time frame for restarting OAC, and any decision making on restarting OAC needs to balance the risks of adverse outcomes. More data are still needed to better elucidate the best time frame to restart OAC therapy after a bleeding event, particularly in AF patient cohorts.

Our systematic review and meta-analysis has some limitations. The main limitation relates to the observational nature of the studies included in the meta-analysis, that did not allow us to establish a direct causal inference between the exposure to OAC and outcomes. Given the inherent nature of the studies included, we reported results with an overall high level of heterogeneity. Also, a certain degree of heterogeneity in the definition of the bleeding index event, represents a limitation to our subgroup analysis, that has to be interpreted cautiously. Moreover, given the small number of studies included and the lack of data about baseline clinical characteristics we could not perform any meta-regression analysis, that could have taken better account of the level of heterogeneity. Beyond this, the limited number of the included studies does not make the I2 a completely reliable measure of the heterogeneity, hence the reason why a Bayesian technique was used, as detailed in the S1 Methods. All the studies included originated from North America or Europe, then extension and generalization of results to other regions is uncertain. Nevertheless, the main conclusions are not invalidated, since all have to be considered as major bleeding events and, the main inclusion criterion of the concomitant OAC therapy use *before* the index event was fulfilled for all patients included. Given the changing landscape of OAC treatment in AF, with the introduction of non-vitamin K antagonist oral anticoagulants, lack of data on these drugs somewhat limits the full generalizability of our results. Nevertheless, vitamin K antagonists are still widely used worldwide. Finally, we cannot exclude a small bias due to the language restriction. Notwithstanding all the limitations provided, considering that the current ESC guidelines support restarting of OAC after major bleeding only on the basis of single observational studies, our work is able to better substantiate the recommendations provided.

5. CONCLUSIONS

In conclusion, this meta-analysis of observational studies indicates that restarting OAC therapy after a major bleeding event in AF was associated with a positive clinical benefit when compared to non-restarting OAC, with a significant reduction in any thromboembolism and all-cause mortality.

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Table 1: Characteristics of Included Studies

Study	Year	Study Type	Study Cohort	Location	N*	Age (Mean)	HAS-BLED	Thromboembolic Risk	Primary Outcomes	FU
Any Major Bleeding										
Hernandez et al.[13]	2017	Retrospective Longitudinal	Insurance Registry	USA	1539	NA	NA	NA	Ischemic Stroke, All-Cause Death	1 year
Intracranial Hemorrhage										
Kuramatsu et al.[14]	2015	Retrospective Longitudinal	Tertiary Care Hospitals	Germany	853 (566†)	74.1 (Mean)	3.0 (Mean)	$CHADS_2$: 2.4 (Mean)	Thromboembolic Events, Recurrent Major Bleeding	1 year
Nielsen et al.[15]	2017	Retrospective Longitudinal	Nationwide Registries	Denmark	2415 (1183‡)	77.1 (Mean)	3.6 (Mean)	CHA_2DS_2-VASc: 3.9 (Mean)	Stroke/SE, Recurrent ICH	279 days
Gastrointestinal Bleeding										
Witt et al.[16]	2012	Retrospective Longitudinal	Administrative Cohort	USA	442 (223†)	74.2	NA	NA	Ischemic Stroke, Thromboembolic Events	90 days
Qureshi et al.[17]	2014	Retrospective Longitudinal	Anticoagulation Clinic	USA	1329	75 (Median)	3 (Median)	$CHADS_2$: 3 (Median)	Thromboembolic Events	2 years
Sengupta et al.[19]	2015	Prospective	Single Center Cohort	USA	197 (115†)	75 (Median)	3 (Median)	$CHADS_2$: 3 (Median)	Thromboembolic Events	90 days

Staerk et al.[18]	2015	Retrospective Longitudinal	Nationwide Registries	Denmark	4602 (730§)	78.3	2.6	CHA_2DS_2-VASc: 3.6	All-Cause Death, Thromboembolic and Major Bleeding Related Hospitalization or Death	2 years

Legend: *numbers in brackets refer to patients included in the meta-analysis; †subgroup of AF patients; ‡propensity score matched subgroup of patients after a 10-week blanking period; §subgroup of patients treated with OAC only before the event and restarted with OAC only; AF= atrial fibrillation; FU= follow-up; ICH= intracranial hemorrhage; NA= not available; NR: non-restarters; OAC= oral anticoagulant; R= restarters; SE= systemic embolism.

FIGURE LEGENDS

Figure 1: Effect of Restarting Oral Anticoagulant on Effectiveness Outcomes

Legend: a) Ischemic Stroke; b) Any Thromboembolic Events; OAC= Oral Anticoagulant; CI= Confidence Interval.

Figure 2: Effect of Restarting Oral Anticoagulant on Safety Outcomes

Legend: a) Recurrent Major Bleeding; b) All-Cause Death; OAC= Oral Anticoagulant; CI= Confidence Interval.

Figure 3: Net Clinical Benefit of Restarting Oral Anticoagulant after Major Bleeding Occurrence.

Legend: CI= confidence interval; NCB= net clinical benefit.

HIGHLIGHTS

Uncertainties exist about restarting oral anticoagulant (OAC) after major bleeding

In particular, evidence in atrial fibrillation (AF) patients is quite scarce

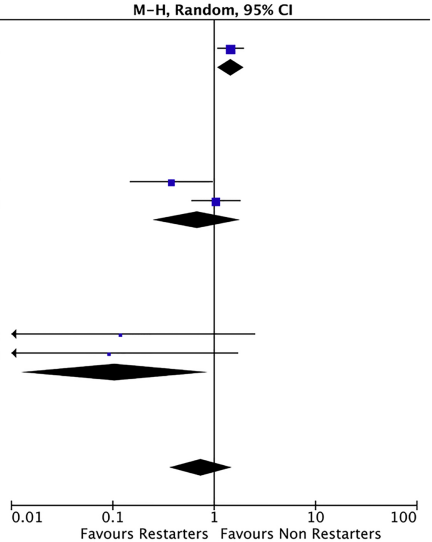
Restarting OAC in AF is associated with a reduction in thromboembolism and death

An increase in risk for recurrent major bleeding was also verified

Overall, restarting OAC in AF is associated with a positive net clinical benefit

a) Any Stroke

Study or Subgroup	OAC Restarters Events	Total	OAC Non Restarters Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Any Major Bleeding						
Hernandez 2017	103	696	90	843	36.3%	1.45 [1.07, 1.97]
Subtotal (95% CI)		**696**		**843**	**36.3%**	**1.45 [1.07, 1.97]**
Total events	103		90			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.42 (P = 0.02)						
1.1.2 Intracranial Hemorrhage						
Kuramatsu 2015	5	110	51	456	22.9%	0.38 [0.15, 0.97]
Nielsen 2017	20	405	37	778	31.2%	1.04 [0.60, 1.82]
Subtotal (95% CI)		**515**		**1234**	**54.1%**	**0.67 [0.25, 1.82]**
Total events	25		88			
Heterogeneity: $Tau^2 = 0.37$; $Chi^2 = 3.35$, df = 1 (P = 0.07); $I^2 = 70\%$						
Test for overall effect: Z = 0.78 (P = 0.44)						
1.1.3 Gastrointestinal Bleeding						
Sengupta 2015	0	71	2	44	4.6%	0.12 [0.01, 2.54]
Witt 2012	0	120	4	103	5.0%	0.09 [0.00, 1.72]
Subtotal (95% CI)		**191**		**147**	**9.6%**	**0.10 [0.01, 0.86]**
Total events	0		6			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.90); $I^2 = 0\%$						
Test for overall effect: Z = 2.10 (P = 0.04)						
Total (95% CI)		**1402**		**2224**	**100.0%**	**0.75 [0.37, 1.51]**
Total events	128		184			
Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 12.91$, df = 4 (P = 0.01); $I^2 = 69\%$						
Test for overall effect: Z = 0.82 (P = 0.41)						
Test for subgroup differences: $Chi^2 = 7.67$, df = 2 (P = 0.02), $I^2 = 73.9\%$						



b) Any Thromboembolic Event

Study or Subgroup	OAC Restarters Events	Total	OAC Non Restarters Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Intracranial Hemorrhage						
Kuramatsu 2015	6	110	68	456	11.6%	0.33 [0.14, 0.78]
Nielsen 2017	10	405	32	778	9.9%	0.59 [0.29, 1.21]
Subtotal (95% CI)		**515**		**1234**	**21.4%**	**0.45 [0.26, 0.78]**
Total events	16		100			
Heterogeneity: $Chi^2 = 1.05$, df = 1 (P = 0.31); $I^2 = 5\%$						
Test for overall effect: Z = 2.86 (P = 0.004)						
1.2.2 Gastrointestinal Bleeding						
Qureshi 2014	90	653	131	676	51.3%	0.67 [0.50, 0.89]
Sengupta 2015	0	71	3	44	2.0%	0.08 [0.00, 1.65]
Staerk 2015	43	511	38	219	22.5%	0.44 [0.27, 0.70]
Witt 2012	0	120	5	103	2.7%	0.07 [0.00, 1.36]
Subtotal (95% CI)		**1355**		**1042**	**78.6%**	**0.56 [0.44, 0.72]**
Total events	133		177			
Heterogeneity: $Chi^2 = 5.79$, df = 3 (P = 0.12); $I^2 = 48\%$						
Test for overall effect: Z = 4.56 (P < 0.00001)						
Total (95% CI)		**1870**		**2276**	**100.0%**	**0.54 [0.43, 0.68]**
Total events	149		277			
Heterogeneity: $Chi^2 = 7.34$, df = 5 (P = 0.20); $I^2 = 32\%$						
Test for overall effect: Z = 5.40 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 0.55$, df = 1 (P = 0.46), $I^2 = 0\%$						

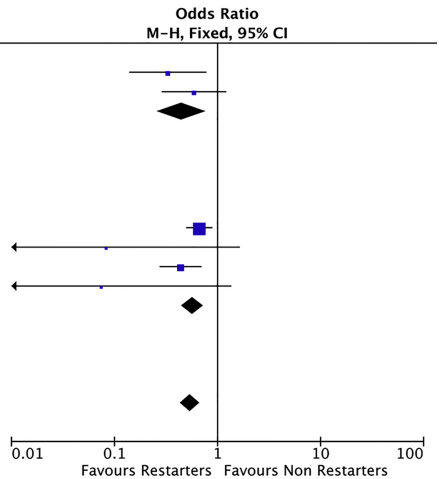
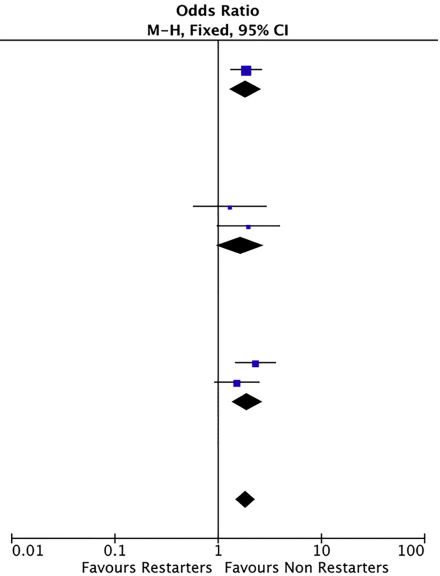


Figure 1

a) Recurrent Major Bleeding

Study or Subgroup	OAC Restarters Events	Total	OAC Non Restarters Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Any Major Bleeding						
Hernandez 2017	83	696	57	843	38.7%	1.87 [1.31, 2.66]
Subtotal (95% CI)		**696**		**843**	**38.7%**	**1.87 [1.31, 2.66]**
Total events	83		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.46 (P = 0.0005)						
1.3.2 Intracranial Hemorrhage						
Kuramatsu 2015	8	110	26	456	8.0%	1.30 [0.57, 2.95]
Nielsen 2017	16	405	16	778	9.0%	1.96 [0.97, 3.96]
Subtotal (95% CI)		**515**		**1234**	**16.9%**	**1.65 [0.97, 2.79]**
Total events	24		42			
Heterogeneity: Chi^2 = 0.56, df = 1 (P = 0.46); I^2 = 0%						
Test for overall effect: Z = 1.85 (P = 0.06)						
1.3.3 Gastrointestinal Bleeding						
Qureshi 2014	61	653	29	676	22.0%	2.30 [1.46, 3.63]
Staerk 2015	74	511	22	219	22.4%	1.52 [0.92, 2.51]
Subtotal (95% CI)		**1164**		**895**	**44.4%**	**1.90 [1.36, 2.67]**
Total events	135		51			
Heterogeneity: Chi^2 = 1.44, df = 1 (P = 0.23); I^2 = 30%						
Test for overall effect: Z = 3.72 (P = 0.0002)						
Total (95% CI)		**2375**		**2972**	**100.0%**	**1.85 [1.48, 2.30]**
Total events	242		150			
Heterogeneity: Chi^2 = 2.21, df = 4 (P = 0.70); I^2 = 0%						
Test for overall effect: Z = 5.42 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 0.21, df = 2 (P = 0.90), I^2 = 0%						



b) All-Cause Death

Study or Subgroup	OAC Restarters Events	Total	OAC Non Restarters Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.4.1 Any Major Bleeding						
Hernandez 2017	32	696	111	843	20.1%	0.32 [0.21, 0.48]
Subtotal (95% CI)		**696**		**843**	**20.1%**	**0.32 [0.21, 0.48]**
Total events	32		111			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.52 (P < 0.00001)						
1.4.2 Intracranial Hemorrhage						
Kuramatsu 2015	9	110	171	456	15.3%	0.15 [0.07, 0.30]
Nielsen 2017	54	405	132	778	21.1%	0.75 [0.53, 1.06]
Subtotal (95% CI)		**515**		**1234**	**36.4%**	**0.34 [0.07, 1.74]**
Total events	63		303			
Heterogeneity: Tau^2 = 1.29; Chi^2 = 17.02, df = 1 (P < 0.0001); I^2 = 94%						
Test for overall effect: Z = 1.29 (P = 0.20)						
1.4.3 Gastrointestinal Bleeding						
Qureshi 2014	187	653	276	676	22.6%	0.58 [0.46, 0.73]
Staerk 2015	87	511	91	219	20.9%	0.29 [0.20, 0.41]
Subtotal (95% CI)		**1164**		**895**	**43.5%**	**0.42 [0.21, 0.83]**
Total events	274		367			
Heterogeneity: Tau^2 = 0.22; Chi^2 = 10.62, df = 1 (P = 0.001); I^2 = 91%						
Test for overall effect: Z = 2.51 (P = 0.01)						
Total (95% CI)		**2375**		**2972**	**100.0%**	**0.38 [0.24, 0.60]**
Total events	369		781			
Heterogeneity: Tau^2 = 0.23; Chi^2 = 31.75, df = 4 (P < 0.00001); I^2 = 87%						
Test for overall effect: Z = 4.10 (P < 0.0001)						
Test for subgroup differences: Chi^2 = 0.43, df = 2 (P = 0.81), I^2 = 0%						

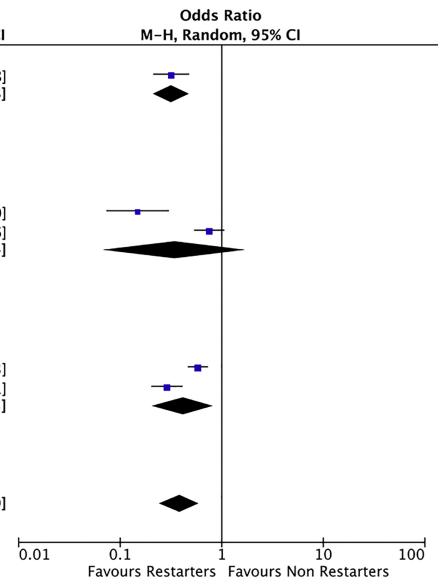
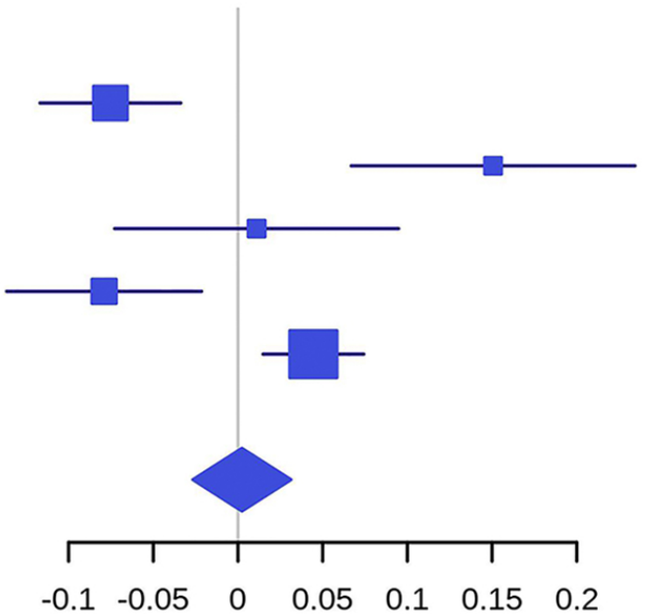


Figure 2

a) NCB Model 1

Study	N	NCB	95% CI	
Hernandez	1539	-0.075	-0.117	-0.034
Kuramatsu	566	0.151	0.067	0.234
Nielsen	1183	0.011	-0.073	0.095
Qureshi	1329	-0.079	-0.137	-0.021
Staerk	1649	0.045	0.015	0.074
Summary		**0.002**	**-0.027**	**0.031**



b) NCB Model 2

Study	N	NCB	95% CI	
Hernandez	1539	0.071	0.04	0.101
Kuramatsu	566	0.323	0.244	0.403
Nielsen	1183	0.192	0.086	0.298
Qureshi	1329	0.046	-0.001	0.092
Staerk	1649	0.201	0.156	0.245
Summary		**0.114**	**0.085**	**0.143**

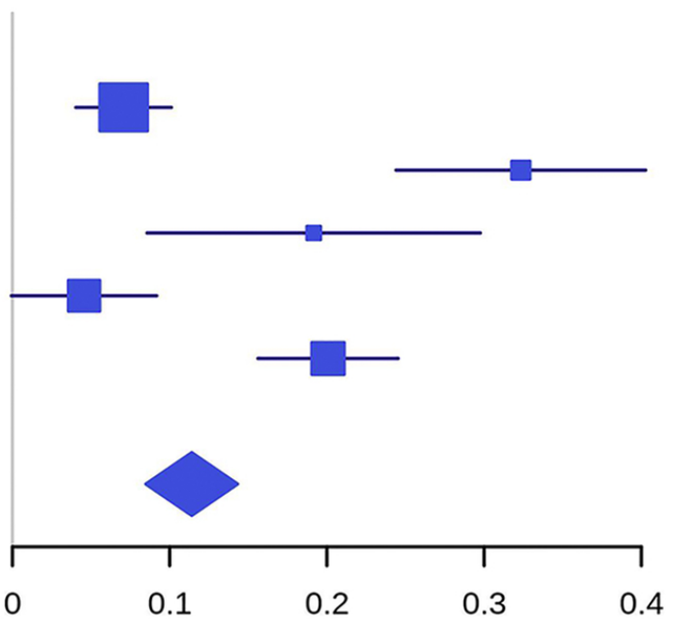


Figure 3